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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,711	09/11/2003	Carl R. Merril	NIH298.1DC1CC1	4758

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EXAMINER	
SNYDER, STUART	

ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
12/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/659,711	MERRIL ET AL.	
	Examiner	Art Unit	
	STUART W. SNYDER	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,22,23 and 31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,22,23 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/16/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/16/2008 has been entered.

Status of the Claims

2. Amendment of Claim 20 and addition of new claims 31-36 in Applicants' filing of 7/16/2008 is acknowledged. Claims 20, 22-23 and 31-36 are pending and examined herein.

Declaration under 37 CFR 1.132

3. The Declaration under 37 CFR 1.132 filed 7/16/2008 is insufficient to overcome the rejection of claims 20 and 22-23 based upon 35 U.S.C. 112, enablement and written description, as set forth in the last Office action because:

Dr. Merril's arguments concerning enablement and written description are that certain small peptides interfere with complement-mediated immune functions, that one can readily make fusion proteins that express host defense-antagonizing peptides on the C-terminus, that viruses that infect animals have evolved mechanisms to evade the immune system, and that one can combine these observations together and arrive at the conclusion that a small peptide

expressed at the end of phage coat protein will imbue the phage with immune escape properties. To further buttress such a contention, Dr. Merril refers to Sokoloff, *et al.* who indeed produced phages that circulate *in vivo* longer than wild-type phage.

With regard to the first aspect of Dr. Merril's arguments, there is no dispute that the genetic techniques presented in the Specification would result in a modified phage displaying the desired peptide. However, there is no evidence presented in the Declaration that the peptide would retain host defense antagonizing activity nor is there a rebuttal in the Declaration of Examiner's contention (see Non-final Rejection mailed 11/20/2006) that the context of the peptide is essential for it's activity. As discussed in that Office Action, it appears that the sequence N-terminal to the "core peptide" has a profound effect on its complement inhibitory activity. Furthermore, the only information that one has regarding the LARSNL in the context of a protein is that it is a substrate for a component of the complement system. Also, the fact that animal viruses have evolved to evade host defense is immaterial to enablement or written description rejections relative to molecular biological construction of immune escape bacteriophages because it does not permit one to envision the specific host defence antagonizing peptides that will delay inactivation of a phage displaying the same.

Finally, with respect to Sokoloff, *et al.*, their successful generation of complement escape mutant bacteriophage is irrelevant to enablement and

written description rejections. In the first place, there is no teaching in the Specification indicating that randomly generated peptides were contemplated to be added to the end of bacteriophage coat proteins. Secondly, none of the mutant virions generated by Sokoloff's group possess sequences similar to those suggested in the Specification. Thus, for reasons of record and those presented herein, the Declaration of Dr. Merril is unpersuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 20, 22-23 and 31-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of producing bacteriophage able to delay inactivation by an animals host defense system. At issue is whether the Specification describes in sufficient detail the specific modification that would delay inactivation of the bacteriophage, delay clearance by a host innate immune system, or survive longer in an animal's body compared to wild-type bacteriophage. There is no dispute that the molecular biological methods per se are adequately described by Applicants and would result in a phage displaying

peptides. However, there is no indication in the Specification or in Applicants' subsequent filings that the prophetic phage actually persists longer in host animals than wild type. At the current time, the only molecular biologic methods that produce phage with relatively longer persistence are those employing random addition of peptides at the C-terminal end of T7 phage (Sokoloff, et al. submitted by Applicants) and the repoduction by Applicants of the phage generated by serial passage in mice. There is no support in the Specification that such methods were contemplated by Applicants but rather specific peptides that were identified by other investigators prior to filing of the Specification of the instant Application possessing complement or other immune component antagonist; for example, the peptide recited in claim LARSNL. Of particular interest to the Examiner is none of the several T7 mutants possessing the host defense-resistant phenotype identified by Sokoloff, *et al.* resemble the peptides proposed by Applicants, *e.g.*, host defense-antagonizing peptides.

With regard to the question of whether or not displaying host defense-antagonizing peptides on the surface of phage would prolong the circulatory life time of the phage, the arguments presented remain unconvincing. The structure of the peptides inserted into or added to the C-terminus of phage surface proteins depends on the sequence of the phage surface protein in the immediate vicinity of the insert or add-on as well as the sequence of the particular added peptide. Such a consideration is very important because the complement-antagonizing peptides were identified as free peptides, not in the context of

proteins or larger macromolecular entities. It is not clear that addition of peptides to the end of proteins would retain the same three dimensional structures as in solution nor is it clear that the peptides would be accessible to host defense entities that they would supposedly antagonize. Indeed, well characterized fusion peptides, such as the poly-His peptides, often function only in the context of the C- or N-terminus of the fusion protein and cloning kits utilizing poly-His to assist in subsequent purification of poly-His containing fusion proteins suggest adding the poly-His moiety to either end to maximize the probability of the cloning and purification strategy.

Furthermore, Schasteen, *et al.* teaches that the context of the inhibitory peptide is important (see esp. Tables 2 and 3, p 1272); for example, in Table 2, peptide 1 has little or no intrinsic inhibitory activity whereas an analogue has complete inhibitory activity of both complement pathways when presented in the context of a "short core" construct. This conclusion is underscored by the data presented in Peake, et al. in that a peptide of the amino acid sequence RSNL had 10 times the inhibitory activity as did LARSNL in the same enzymatic assay. Thus, it would be difficult if not impossible to predict *a priori* that a phage construct would have host defense inhibitory activity because of the dependence of such activity on the immediate context of the peptide sequence. Additional considerations of steric hindrance by phage coat protein for access of complement convertases to the putative inhibitory peptides are not addressed by Applicant.

In sum, although there is adequate description of preparation techniques, there is insufficient information in the Specification or in the art as a whole, at the time the instant Application was filed, that addition of host defense-antagonizing peptides to the phage surface proteins would actually result in longer circulating phage. Therefore, rejection of claims 20 and 22-23 are **maintained** under 35 U.S.C. 112, 1st paragraph with respect to written description; claims 31-36 are also rejected under 35 U.S.C. 112, 1st paragraph.

5. Claims 20, 22-23 and 31-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. There is no dispute that the Specification fully enables construction of phages with peptides expressed on the surface proteins of such phages. However, as described in section 3 above, there is no teaching in the Specification of how present the host defense-antagonizing peptides so as to imbue the resultant phages with host defense eluding capacity. As described above, it is clear that the context of the host defense-antagonizing peptides in important; there is no teaching in the Specification nor in the art at the time of filing of the instant Specification which contextual factors are sufficient for the defense-antagonizing peptides to retain their activity. Indeed, Schasteen, *et al.* teaches away from peptides of increasing length by showing a decrease in activity of LARSNL *vs.* RSNL, as discussed above. Therefore, rejection of claims 20 and 22-23 are **maintained** under 35 U.S.C. 112, 1st paragraph with respect to written description; claims 31-36 are also rejected under 35 U.S.C. 112, 1st paragraph.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STUART W. SNYDER whose telephone number is (571)272-9945. The examiner can normally be reached on 9:00 AM-5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mary E Mosher/
Primary Examiner, Art Unit 1648

Stuart W Snyder
Examiner
Art Unit 1648

sws